REMARKS

Claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46- 47 and 50-51 were pending. No amendments have been made to the claims, thus Claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46- 47 and 50-51 are currently pending.

THE CLAIMED INVENTION

The invention is directed to novel methods to replenish glutathione (GSH) in a cell using sulfhydryl protected glutathione prodrugs which provides preformed GSH to cells and bypasses the cellular GSH synthesis pathway. Before Applicants' invention, no one taught or suggested using sulfhydryl protected glutathione prodrugs to replenish GSH in a subject. Applicants were the first to use sulfhydryl protected glutathione prodrugs as a readily accessible source of GSH when preformed GSH is released from the prodrug by reduction. Applicants were the first to provide experimental evidence that an exogenously administered sulfhydryl protected glutathione prodrug (e.g., L-CySSG) can protect the liver from the toxic insult of acetaminophen, a drug known to severely deplete GSH and elicit hepatotoxicity.

REJECTION UNDER 35 U.S.C. §103(a)

The Examiner rejected claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46-47 and 50-51 as unpatentable over Shirota et al., Jonas et al. and Bender et al.

Applicants respectfully disagree.

A. THE LEGAL STANDARD FOR ESTABLISHING OBVIOUSNESS UNDER 35 U.S.C. §103

The legal standard for a rejection under §103 is as follows. As set forth in MPEP §2143:

> *To establish a* prima facie *case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicants' disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 148 USPQ 459, 467 (1966). To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the Applicants' achievement, that must establish the obviousness of the combination.

The teachings of the references, their relatedness to the field of the Applicants' endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all

relevant considerations. See *In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). When the references are in the same field as that of the Applicants' invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the Applicants, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

B. APPLICANTS HAVE MET THE LEGAL STANDARD FOR NONOBVIOUSNESS

The Office rejected the pending claims under 35 U.S.C. §103(a) in view of the combination of Shirota et al., Jonas et al., and Bender et al. The Office took the position that one skilled in the art would have been motivated to substitute CySSG (as described in Jonas et al. and whose use is encompassed by the claimed methods) for CySSME (as described in Shirota et al.) to produce GSH and reduce oxidative stress e.g., caused by acetaminophen toxicity. Further, the Office took the position that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention (i.e., a method for reducing oxidative stress using a sulfhydryl protected glutathione prodrug) by making the substitution (page 4, first paragraph).

Applicants respectfully disagree. The cited art do not teach or suggest substitution of CySSG for CySSME for any reason, much less substitution of CySSG for CySSME for the production of GSH and the reduction of oxidative stress as claimed.

Shirota et al.

Shirota et al. teach that (1) three structurally diverse types of L-cysteine prodrugs (NOT sulfhydryl protected glutathione prodrugs), two of them sulfhydryl-protected (e.g., CySSME), can reduce acetaminophen induced hepatic toxicity as measured by plasma alanine aminotransferase (ALT) activity and (2) maintenance of glutathione homeostasis can protect hepatic AdoMet sythetase activity (Abstract). The L-cysteine prodrug CySSME is a mixed disulfide of cysteine and mercaptoethanol and is dependent on enzymatic reduction of its disulfide bond to release cysteine (page 5, 2nd column, 3rd paragraph). Shirota et al. also teach that hepatoprotection by the cysteine generated from various cysteine prodrugs is due to enhanced GSH synthesis and maintenance of hepatic GSH homeostasis (page 5, 2nd column, last paragraph).

Shirota et al. do not teach use of any sulfhydryl protected glutathione prodrug let alone use of a sulfhydryl protected glutathione prodrug to provide glutathione directly to cells without *de novo* glutathione synthesis or to reduce oxidative stress in a cell. L-Cysteine prodrugs and sulfhydryl protected glutathione prodrugs are not equivalents; reduction of sulfhydryl protected glutathione prodrugs releases preformed glutathione (as well as L-cysteine in the case of L-CySSG), while L-cysteine prodrugs (such as CySSME) release L-cysteine (specification at page 9, lines 3-6).

Jonas et al.

Jonas et al. teach that cysteine-glutathione mixed disulfide (CSSG) treatment of cystinotic fibroblasts, fibroblasts from patients heterozygous for cystinosis and normal (i.e., non-cystinotic) fibroblasts lead to an increase in cystine levels in the cells. Heterozygous and normal fibroblasts rapidly cleared the accumulated cystine when CSSG treatment was removed while cystinotic fibroblasts retained cystine. (abstract)

Jonas et al. teach that CSSG provides "a soluble source of cyst(e)ine" for cells (page 4442, 1st column, 2nd paragraph).

Jonas et al. do not teach use of any sulfhydryl protected glutathione prodrug (e.g., CSSG), let alone a sulfhydryl protected glutathione prodrug to release preformed glutathione to cells or to reduce oxidative stress in a cell.

Bender et al.

Bender et al. studied the mechanism of cystine uptake in astrocytes and found that astrocytes transport cystine through a similar, if not identical, system used to transport glutamate (Abstract). Bender et al. also teach that cellular uptake of cystine is the rate-limiting step in the biosynthesis of glutathione (Abstract). Cystine, after transport into cells, is reduced to cysteine, a precursor of glutathione. Thus, cystine, via cysteine, is required for maintaining cellular levels of glutathione. Glutathione protects cells against oxidative stress and various toxins. (Abstract)

However, Bender et al. do not teach use of any sulfhydryl protected glutathione prodrug, let alone a sulfhydryl protected glutathione prodrug to release preformed glutathione to cells or to reduce oxidative stress in a cell.

The Office alleges that Bender's teaching (that cystine is reduced to cysteine which is used to synthesize glutathione) provides a nexus between the administration of CySSG (as taught by Jonas et al.) and the production of GSH for the reduction of oxidative stress with a L-cysteine prodrug (as taught by Shirota et al.) (last paragraph on page 3 of the outstanding Office Action). Thus, the Office concludes that it would have been obvious to substitute CySSG (a sulfhydryl protected glutathione prodrug) for CySSME (a L-cysteine prodrug) (first paragraph on page 4 of the outstanding Office Action).

This reasoning falsely assumes (1) that there is similarity between CySSG and CySSME which would suggest their interchangeability; and (2) that there is motivation to use sulfhydryl protected glutathione prodrug instead of a cysteine prodrug; and (3) that motivation exists to use sulfhydryl protected glutathione prodrug to reduce oxidative stress. Applicants respectfully reject these arguments.

The Rejection is Based on Inapplicable Legal Standards

The rejection of the Patent Office appears to be contrary to the guidance provided by the Federal Circuit as to how references can be combined.

In order for an obviousness rejection to be proper, the prior art itself must suggest the desirability of making the required modification or combination. As the Court of Appeals for the Federal Circuit has held:

> The mere fact that the prior art could be so modified would not have made the modification obvious unless the ***prior art suggested the desirability of the modification.*** (emphasis added)[1].

Here, no such suggestion is presented by the cited publications. It is clear that "obvious to try" is not the appropriate legal standard. (In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987; In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

There must be some motivation in the art to make the combination. (In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Contrary to the Office's statement on page 4 of the outstanding Office Action, there is no motivation to substitute CySSG for CySSME for reducing oxidative stress in a cell.

[1] In re Gordon, 221 U.S.P.Q. 1125, 1127.

CySSG and CySSME do not share a common utility and function (In re Lalu and Foulletier 747 F.2D 703, 223 USPQ 1257 (Fed. Cir. 1984)).

CySSG is a sulfhydryl protected glutathione prodrug while CySSME is sulfhydryl protected cysteine prodrugs (specification at page 3, lines 9-12). CySSG is a mixed disulfide of L-cysteine and glutathione. When reduced, CySSG releases a preformed glutathione as well as L-cysteine. The L-cysteine is a precursor for *de novo* glutathione synthesis. Thus, CySSG produces **two** glutathiones; the first glutathione is released from CySSG by reduction making it immediately available to the cell; the second glutathione is *de novo* synthesized by the cell from the L-cysteine that was released by CySSG (specification at page 9, first paragraph).

CySSME is a mixed disulfide of L-cysteine and mercaptoethanol. Only a single glutathione can be produced from CySSME, this via *de novo* synthesis.

Sulfhydryl protected glutathione prodrugs such as CySSG and sulfhydryl protected cysteine prodrugs such as CySSME do not share a common utility and function. Unlike sulfhydryl protected cysteine prodrugs, administration of a sulfhydryl protected glutathione prodrug to a cell provides a source of preformed glutathione independent of the cell's endogenous GSH biosynthesis pathway.

Sulfhydryl protected glutathione prodrugs provide a readily accessible source of GSH to a cell due to the preformed GSH that is released from the prodrug under reducing conditions without the need for *de novo* biosynthesis of GSH. As an organism ages, the GSH synthesis pathway becomes impaired leading to a decrease in GSH biosynthesis. Sulfhydryl protected glutathione prodrugs such as CySSG deliver preformed GSH to the cell whether or not the GSH biosynthesis pathway is functional.

Additionally, to alleviate aggressive oxidative stress, for example after acetaminophen administration, a source of GSH such as a sulfhydryl protected glutathione prodrug can be provided expeditiously to a cell. Prior to the present invention, it was not obvious that sulfhydryl protected glutathione prodrugs were a readily available and efficient source of GSH to a cell nor to administer a sulfhydryl protected glutathione prodrug such as CySSG since, among other things, it had not been known whether the enzymatic reduction (or enzyme-catalyzed thiol-disulfide interchange reaction) velocity of CySSG would be sufficiently fast and efficient to replenish GSH.

The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430, cited in MPEP §2143.01. There must be a reason or suggestion in the art for modifying the prior art other than the knowledge learned from applicants' disclosure[2]. However, the cited references provide none. The primary reference, Shirota et al., teach that prodrugs of L-cysteine, one of them being CySSME, can protect hepatic AdoMet synthetase activity and reduce acetaminophen induced hepatic toxicity by providing L-cysteine. The secondary references do not teach or suggest what the primary reference fails to teach, namely, the use of sulfhydryl protected glutathione prodrug (e.g., CSSG) to deliver preformed glutathione to cells or to reduce oxidative stress in a cell. Further, and contrary to the Office's statement, there would have been no motivation to substitute CySSG for CySSME because they are not equivalents. Accordingly, the combination of the primary and secondary references does not and cannot render obvious the claimed methods.

[2] *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

Even if "Obvious to Try" is the Appropriate Legal Standard, One of Ordinary Skill in the Art would not Expect Successful Results

Although obviousness under 35 U.S.C. §103 does not require absolute predictability of success, 35 U.S.C. §103 does require a reasonable expectation of success to find obviousness. (In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)).

Given the state of the art, there would have been no reasonable expectation that one would be able to produce the claimed method by simply substituting a sulfhydryl protected glutathione prodrug for a cysteine prodrug, sufhydryl-protected or otherwise.

CONCLUSION

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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